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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,300	02/24/2004	Roy A. Black	016761-0171	5048

7590 02/04/2008

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,300	BLACK ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,11,12,14-22 and 29-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11,12,14-22 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/07 has been entered.

[2] Claims 1-5, 7-9, 11-12, 14-22, and 29-36 are pending in the application.

[3] Applicant's amendment to the claims, filed on 10/29/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Applicant is reminded of the amendment practice according to 37 CFR 1.121. See particularly claim 22, which uses the status identifier "(Previously presented)", where the claim appears to have been amended relative to the prior version.

[4] Applicant's amendment to the specification, filed on 10/29/07, is acknowledged.

[5] Receipt of a substitute sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, and an amendment directing entry of the sequence listing into the specification, all filed on 7/27/07, is acknowledged.

[6] Applicant's arguments filed on 10/29/07 in response to the Office actions mailed on 2/27/07 and 8/6/07 have been fully considered and are deemed to be persuasive to

overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

[8] Applicant's request for status clarification under the proposed changes to claims and continuations at pp. 9-10 of the instant remarks is acknowledged. However, as such proposed changes were not effected on 11/1/07, the instant application has been processed and examined according to the rules and procedures in effect on 10/31/07.

Sequence Compliance

[9] The specification is objected to as failing to comply with the sequence requirements. As noted in the prior Office action, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence

Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly the disclosed Table 1 at pp. 37-74 of the specification containing a list of atomic coordinates representing the disclosure of an amino acid sequence. Applicant should identify this sequence by a proper sequence identifier.

Claim Objections

[10] Claim 29 is objected to in the recitation of "polynucleotide encoding comprises" and it is suggested that, *e.g.*, "comprises" in the noted phrase be deleted.

[11] Claim 36 is objected to in the recitation of "the crystalline form the crystalline form" and it is suggested that, *e.g.*, one occurrence of "the crystalline form" in the noted phrase be deleted.

Claim Rejections - 35 USC § 112, Second Paragraph

[12] Claim(s) 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-5 are confusing in that it is unclear as to the intended scope of TACE polypeptides that are encompassed by the claims. According to 37 CFR 1.75(c), "Claims in dependent form shall be construed to include all the limitations of the claim

incorporated by reference into the dependent claim". The composition of claim 4 is limited to a polypeptide expressed from a polynucleotide encoding residues 1-477 of SEQ ID NO:8. However, claim 5, which should "include all the limitations of the claim incorporated by reference into the dependent claim", is drawn to a *variant* of residues 1-477 of SEQ ID NO:8. This is confusing because: 1) the recited polypeptide of claim 5 does not include all the limitations of the polypeptide recited in claim 4 and 2) the limitations of claim 5 would require that the polypeptide as recited in claim 4 encompass variants of residues 1-477 of SEQ ID NO:8.

RESPONSE TO ARGUMENT: Applicant argues (p. 12 of the instant remarks) claim 5 has been amended to clarify that the amino acid sequence of SEQ ID NO:8 has been further altered to include additional substitutions and amino acid sequences.

Applicant's argument is not found persuasive. The TACE polypeptide of the composition of claim 4 would not appear to encompass variants within residues 1-477 of SEQ ID NO:8. However, since "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim" and because claim 5 limits the polypeptide of the composition of claim 4 to having substitutions at positions 266 and 452 of SEQ ID NO:8, claim 4 should encompass variants of residues 1-477 of SEQ ID NO:8. It is suggested that applicant clarify the scope of intended polypeptides of the composition of claims 4-5.

[13] The rejection of claims 14 and 30 under 35 U.S.C. 112, second paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was

fully explained in a prior Office action. See paragraph 13, part b at p. 5 of the Office action filed on 2/27/07. Claims 34-36 are included in the instant rejection. Thus, claims 14, 30, and 34-36 are rejected herein.

RESPONSE TO ARGUMENT: Applicant argues (p. 12, bottom of the instant remarks) the rejection is obviated by amendment.

Applicant's argument is not found persuasive. Claims 14, 30, and 34 (claims 35-36 dependent therefrom) are confusing in the recitation of "the crystalline form of the TACE polypeptide has the structure coordinates according to Table 1", "the crystal of the TACE polypeptide has the structure coordinates according to Table 1", and "the crystalline form...has the structure coordinates according to Table 1", respectively, as it would appear from the language of the claims that the crystalline form or the crystal has the structural coordinates of Table 1, where a skilled artisan would recognize that it is the TACE polypeptide of the crystal or crystalline form that has the structural coordinates of Table 1, particularly as the structural coordinates provide the Cartesian coordinates for atoms of the amino acids of a TACE polypeptide. It is suggested that applicant clarify the meaning of the claims.

[14] Claim(s) 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 (claim 21 dependent therefrom) is unclear in the recitation of "the solution comprising the TACE polypeptide and the binding partner is at a concentration

of..." as it is unclear as to what component of the solution has the recited concentration. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[15] The new matter rejection of claims 15-16 and 18-21 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 14 beginning at p. 6 of the Office action filed on 2/27/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 13, top of the instant remarks): 1) adequate written description for newly added claim limitations does not require *in haec verba* support; 2) the specification discloses three species of crystallization buffers, Buffers B, C, and D, which all comprise sodium citrate; and 3) these three representative species of crystallization buffers are sufficient to represent the recited genus of crystallization buffers.

Applicant's argument is not found persuasive. The examiner acknowledges there is no *in haec verba* requirement, however, MPEP 2163.I.B makes clear that "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure". According to MPEP 2163.II.B, "The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117".

According to applicant, support for claim 15 can be found at pp. 4, 16, and 33-34 (instant remarks at p. 13, bottom). There is no dispute that the specification discloses three representative species of buffers with sodium citrate that achieved TACE protein crystallization – Buffers B, C, and D. Each of these buffers has a defined formulation with each component of the formulation having a specific concentration. At the time of the invention, it was well-known in the art that the composition of a crystallization buffer was *critical* to achieving protein crystallization. See, *e.g.,* Branden et al. (cited in the PTO-892 filed on 7/25/06), which teaches "The formation of crystals is also critically dependent on a number of different parameters, including...the nature of the solvent and precipitant as well as the presence of added ions..." (p. 375). As such, a skilled artisan would recognize that each of the elements of Buffers B, C, and D and its corresponding concentration is critical for TACE protein crystallization.

In this case, applicant takes the position that the genus of buffers comprising sodium citrate at any concentration and any pH alone or in combination with any other component(s) at any concentration(s) is supported by the specification's disclosure of three representative species of buffers that achieve TACE protein crystallization – Buffers B, C, and D (see, *e.g.,* pp. 33-34 of the specification). MPEP 2163.05.I states, "A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement". Here, although applicant does not appear to *expressly* disclose crystallization buffer composition and component concentration as being critical to TACE protein crystallization, in view of the state of the art at the time of the invention, a

skilled artisan would recognize that crystallization buffer composition and component concentration is critical to achieving protein crystallization. Thus, the examiner maintains the position that the three disclosed species of crystallization buffers - Buffers B, C, and D - fail to provide adequate descriptive support for a crystallization buffer comprising sodium citrate at any concentration and any pH alone or in combination with any other component(s) at any concentration(s) that achieves crystallization of a TACE polypeptide.

[16] The written description rejection of claims 1-5, 7-9, 11-12, 14-22, and 29-31 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 15 beginning at p. 7 of the Office action filed on 2/27/07. Newly added claims 32-36 have been included in the instant rejection for reasons that follow. Thus, claims 1-5, 7-9, 11-12, 14-22, and 29-36 are rejected herein.

RESPONSE TO ARGUMENT: With respect to claims 1 and 22, applicant argues (beginning at p. 14, bottom of the instant remarks): 1) the crystalline form has been limited to recite space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°; 2) amended claims 1 and 22 are "almost identical in scope" to hypothetical claim 1 of Case 4 of the Trilateral Report; and 3) amended claims 1 and 22 are also similar to claim 1 of Case 4 of the Trilateral Report by being drawn to a known protein with recited unit cell dimensions, wherein the specification discloses how to make crystals of the protein.

Applicant's argument is not found persuasive. The examiner acknowledges the amendment to claims 1 and 22 to recite space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°. However, the examiner maintains the position that the specification fails to adequately describe the claimed composition, particularly with respect to the genus of TACE polypeptides that form a crystal having the recited space group and unit cell dimensions.

In contrast to claim 1 of Case 4 of the Trilateral Report, the genus of compositions encompasses crystalline TACE polypeptides and hydroxamate-based binding partners with undefined structure. As noted in prior Office actions, the single disclosed representative species of compositions comprising crystalline polypeptides fails to reflect the substantial variation among the species of the genus, particularly with respect to the structures of the TACE polypeptide and the hydroxamate-based binding partner. In this case, the specification discloses only a single representative species of the genus of recited crystalline forms of a TACE polypeptide, *i.e.,* TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m-ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°. That the specification discloses *only* these representative species appears to be undisputed by applicant.

Other than these representative species, the specification fails to disclose any additional species of the genus of crystalline TACE proteins, optionally in complex with any hydroxamate-based binding partners, and crystallization conditions, which encompass widely variant species. Based on the claims and the disclosure of the specification, it would appear that the genus of TACE polypeptides of the crystalline form are not limited to the single TACE polypeptide that achieved crystallization. See, *e.g.,* claim 4 and the genus of hydroxamate-based binding partners would appear to encompass any "binding partner" that is based upon a hydroxamate structure (see Appendix A). As such, each genus encompasses widely variant species of "TACE" polypeptides and "hydroxamate-based" binding partners.

As noted above, it was well-known at the time of the invention that protein crystallography was a highly unpredictable art. See, *e.g.,* the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out, trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on

to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." See also the cited teachings of Branden et al., Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06. That protein crystallography was highly unpredictable does not appear to be disputed by applicant.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". "[F]or inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession". Given the high level of unpredictability associated with protein crystallography and the lack of description of a representative number of species to reflect the variation among members of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Addressing dependent claims 2-14 and 29-36, applicant argues these claims further define the relevant structural characteristics of the genus and a skilled artisan would recognize that applicant was in possession of the genus at the time of the invention. Applicant argues the TACE polypeptide disclosed in the specification is representative of the genus because: 1) the recited polypeptide is "similar to a reference sequence"; 2) a skilled artisan could envisage all members of the genus of "hydroxamate-based binding partners"; and 3) the specification discloses a method for crystallizing a polypeptide encompassed by the claims.

Applicant's argument is not found persuasive. The examiner acknowledges the limitations of claims 2-5, 7-9, 11-12, 14, 29-36. However, the examiner maintains the position that the specification fails to adequately describe the claimed composition, particularly with respect to the genus of TACE polypeptides and hydroxamate-based binding partners that form a crystal having the recited space group and unit cell dimensions. Claims 4-5, 29, and 32 limit the TACE polypeptide to being the "expression product" of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8. However, it is noted that since the polynucleotide of the claim is open to encoding any additional amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8, the TACE polypeptide of these claims can have any additional amino acids added thereto. Put another way, the claim has been interpreted as requiring that the polynucleotide encode *at least* residues 1-477 of SEQ ID NO:8, but can additionally

encode amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8. Also, with respect to claims 7, 22, 32, it is noted that the genus of "hydroxamate-based" binding partners is interpreted as encompassing any compound having a hydroxamate group (see Appendix A).

As noted above, the single disclosed representative species of compositions comprising crystalline polypeptides fails to reflect the substantial variation among the species of the genus, particularly with respect to the TACE polypeptide, the hydroxamate-based binding partner, and the crystallization conditions. In this case, the specification discloses only a single representative species of the genus of recited crystalline forms of a TACE polypeptide, *i.e.,* TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°. Also, the specification discloses only three representative species of crystallization buffers that result in crystallization of a TACE polypeptide, *i.e.,* Buffers B, C, and D. That the specification discloses *only* these representative species appears to be undisputed by applicant.

Other than this single representative species, the specification fails to disclose any additional species of the genus of crystalline TACE proteins, optionally in complex

with any hydroxamate-based binding partners, which encompass widely variant species. As noted by Branden et al. (*supra*), "The formation of crystals is also critically dependent on a number of different parameters, including...added...legends to the protein" and McPherson points out that trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by "no more than one or just a few amino acids" can result in significant influences upon the change in which variables are important for successful crystallization. See also the cited teachings of Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06. That protein crystallography was highly unpredictable, even among proteins that are structurally similar with respect to their amino acid sequences does not appear to be disputed by applicant.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Given the high level of unpredictability associated with protein crystallography and the lack of description of a representative number of species to reflect the variation among members of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Addressing claims 15-21, applicant argues claim 15 has been limited to recite a structural feature of the genus of TACE polypeptides that is shared by all members of the genus and allows the skilled artisan to "readily envision" the claimed invention. Applicant argues the TACE polypeptide disclosed in the specification is representative of the genus because: 1) the recited polypeptide is "similar to a reference sequence" and 2) the specification discloses a method for crystallizing a polypeptide encompassed by the claims. Applicant further argues the genus of hydroxamate-based binding partners is adequately described since this "structural definition" allows a skilled artisan to "readily envision" all members of the genus and a single representative species of the genus is disclosed in the specification. Applicant reiterates the above argument traversing the new matter rejection.

Applicant's argument is not found persuasive. The examiner acknowledges the amendment to claim 15. However, the examiner maintains the position that the specification fails to adequately describe the claimed crystallization method, particularly with respect to the genus of TACE polypeptides, hydroxamate-based binding partners, and crystallization conditions that are combined to achieve a method of crystallization of a TACE polypeptide. While claim 15 limits the TACE polypeptide to being the expression product of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8, it is noted that since the polynucleotide of the claim is open to encoding any additional amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8, the TACE polypeptide of these claims can have any additional amino acids added thereto. Put another way, the claim has been interpreted as requiring that

the polynucleotide encode *at least* residues 1-477 of SEQ ID NO:8, but can additionally encode amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8. Also, with respect to hydroxamate-based binding partner, it is noted that the genus of "hydroxamate-based" binding partners is interpreted as encompassing any compound having a hydroxamate group (see Appendix A). Further, regarding the genus of buffers comprising sodium citrate, it is noted that this genus of buffers encompasses buffers with sodium citrate alone, optionally having any additional components, wherein the sodium citrate and optional additional components have undefined concentration(s) at any pH.

As previously noted, the specification discloses only a single representative species of methods for achieving crystallization of a TACE polypeptide, *i.e.*, Example 2 at pp. 33-34 of the instant specification, using a specific TACE polypeptide, *i.e.*, TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells co-crystallized with a specific hydroxamate-based binding partner, *i.e.*, N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine under specific crystallization conditions, *i.e.*, those conditions as set forth at pp. 33-34 of the specification.

Other than this representative species, the specification fails to disclose any additional species of methods for crystallizing any other TACE polypeptide with any other hydroxamate-based binding partner under any other crystallization conditions as

encompassed by the claims, which encompass widely variant species. As noted by the references of Branden et al., Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06 and McPherson (*supra*), protein crystallization is a highly unpredictable art and even a single amino acid difference between polypeptides can alter protein crystallization. That protein crystallography was highly unpredictable, even among proteins that are structurally similar with respect to their amino acid sequences does not appear to be disputed by applicant.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Given the high level of unpredictability associated with protein crystallography and the lack of description of a representative number of species to reflect the variation among members of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[17] The scope of enablement rejection of claim(s) 1-5, 7-9, 11-12, 14-22, and 29-31 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 16 beginning at p. 11 of the Office action filed on 2/27/07. Newly added

claims 32-36 have been included in the instant rejection for reasons that follow. Thus, claims 1-5, 7-9, 11-12, 14-22, and 29-36 are rejected herein.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 18, bottom of the instant remarks) claims 1 and 22 are limited to reciting a specific space group and unit cell dimensions, which is commensurate in scope with claim 1 of Case 4 of the Trilateral Report, and in view of the specification's disclosure of how to make the claimed crystals. Addressing claims 15 and 32-36, applicant argues the claims are limited by amendment to recite a specified TACE sequence and claims 32-36 specify the space group and unit cell dimensions. Applicant argues the disclosed crystal and crystallization method are commensurate in scope with the claimed invention because: 1) the recited polypeptide is "similar to a reference sequence"; 2) the specification discloses a method for crystallizing a polypeptide encompassed by the claims; and 3) the specification discloses a "hydroxamate-based" binding partner as encompassed by the claims.

Applicant's argument is not found persuasive. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content

of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1, 7, and 22 are drawn to a composition comprising a crystalline form of a TACE polypeptide, optionally in complex with a "hydroxamate-based" binding partner, wherein the structure(s) of the TACE polypeptide and/or "hydroxamate-based" binding partner is/are unlimited. Claims 4-5, 29, and 32 limit the TACE polypeptide to being the expression product of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8. However, it is noted that since the polynucleotide of the claim is open to encoding any additional amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8, the TACE polypeptide of these claims can have any additional amino acids added thereto. Put another way, the claim has been interpreted as requiring that the polynucleotide encode *at least* residues 1-477 of SEQ ID NO:8, but can additionally encode amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8. Also, with respect to claims 7, 22, and 32, it is noted that the genus of "hydroxamate-based" binding partners is interpreted as encompassing any compound having a hydroxamate group (see Appendix A). Claim 15 is so broad as to encompass a method for crystallizing the expression product of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8, wherein the "expression product" can have any additional N-terminal and/or C-terminal amino acids as noted above, the structure of the "hydroxamate-based" binding partner is unlimited, and, with the exception of requiring the crystallization buffer to comprise sodium citrate at any concentration and any pH,

the buffer can comprise any other components at any concentrations. The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m-ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 using crystallization buffer D, *i.e.,* 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol.

The nature of the invention: The nature of the invention is a TACE polypeptide in "crystalline form", wherein the crystal is useful for determining by X-ray crystallography the 3-D structure of the TACE polypeptide for use in identifying potential compounds that associate with TACE. See, *e.g.,* p. 2, lines 17-24.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. The reference of Branden et al. (cited in the PTO-892 mailed on 7/25/06) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is

impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. (cited in the PTO-892 mailed on 7/25/06) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (cited in the PTO-892 mailed on 7/25/06), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). In view of these teachings, there is no expectation that a skilled artisan can use the disclosed crystallization conditions to achieve diffraction quality crystals of other TACE polypeptides. Also, Wiencek (cited in the PTO-892 mailed on 7/25/06) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging

between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et al.* teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also the teachings of McPherson as set forth above. Applicant does not appear to dispute the objective evidence of these references. When these teachings are taken as a whole, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other TACE polypeptides optionally having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using *any* crystallization parameters as encompassed by the claims. Further, it is noted that the asserted utility of the claimed crystal is for determination of the structure of TACE for structure based design of TACE inhibitors (p. 2, first full paragraph), which is undisputed by applicant, and it is highly unpredictable as to whether mutant and variant TACE polypeptides will maintain a three-dimensional structure that is equivalent to wild-type TACE for design of biologically relevant TACE inhibitors.

The amount of direction provided by the inventor; The existence of working examples: As noted above, the specification discloses the utility of the claimed crystal is in the determination of the 3-D structure of TACE (p. 2, first full paragraph), which, as acknowledged by Branden et al. at p. 374, requires a diffraction-quality crystal. Applicant does not dispute this position. In this case, the specification discloses only a single working example of such a diffraction quality crystal and method of making

thereof, *i.e.*, a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol. Other than this single working example of a crystal and method for making, the specification fails to provide guidance for crystallizing other polypeptides as encompassed by the claims with an expectation of obtaining diffraction-quality crystals optionally having the recited space group and/or unit cell dimensions. It should be noted that the claims encompass crystals of mutant and variant TACE polypeptides and the specification fails to provide guidance for using those crystals that do not represent biologically relevant TACE polypeptides. Thus, the guidance and working examples as disclosed in the specification fail to remedy the high level of unpredictability that is supported by the references cited above. As noted above and undisputed by applicant, the specification discloses the use of the claimed crystal as being for determination of the 3-D structure of TACE (p. 2, first full paragraph). While applicant may argue the claims do not require diffraction quality crystals, it is noted that the specification fails to provide guidance regarding the use of a TACE crystal that is not of diffraction quality. Also of note is that while the specification discloses crystallization bufferers A, B, C, and D (specification at pp. 33-34), it appears that only crystallization

buffer D "allowed the production of crystals *suitable for X-ray data collection*" (specification at p. 34, lines 5-6).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, it was not routine in the art to screen all TACE polypeptide variants as encompassed by the claims, optionally complexed with any ligand for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystal and polypeptide compositions as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Beginning at p. 20 of the instant remarks, applicant characterizes the claimed invention, noting *inter alia* the disclosure describes how to make a crystal of SEQ ID NO:8 and the catalytic domain was shown to fold in a relatively stable conformation containing at least three intermolecular disulfide bonds. According to applicant, the TACE polypeptide folded into a compact structure capable of packing productively in the crystal lattice and forming good lattice contacts. Applicant asserts that at the time of the invention, variants of a protein with known crystallization parameters were likely to readily crystallize with similar crystal structures as long as the variations did not affect intermolecular crystal contacts or amino acids important for stability, relying on the reference of Itoh et al. According to applicants, even mutations that had an effect in altering protein stability were found to crystallize with similar crystallization parameters as the native protein, relying on Sauer et al. Applicant argues that once TACE variants are constructed it would require no more than routine experimentation to crystallize the variants using the disclosed method.

Applicant's argument is not found persuasive. Initially, it is noted that, contrary to applicant's assertion, the specification teaches the working example of crystallizing a *variant* of SEQ ID NO:8 with Ser266Ala and Asn452Gln substitutions and a Gly-Ser-(His)6 tag at the C-terminus. Also, with regard to applicant's assertions regarding the disclosed TACE polypeptide of the crystal as being "relatively compact", "capable of packing productively", and "forming good lattice contacts", it is noted that applicant fails to point to any objective evidence of record to support such arguments. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of

evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)".

Applicant relies on the references of Itho and Sauer to support the above position. It is of note that none of the variant crystals of Ihto and Sauer maintain the identical unit cell dimensions of the wild-type polypeptide to the extent required in claims 1, 22, and 36, particularly with respect to the dimensions of vectors a, b, and c. See particularly p. 2264, Table 2 of Ihto and p. 2395, Table III of Sauer. As such, Ihto and Sauer actually support the examiner's position regarding a high level of unpredictability. Moreover, it is noted that the references of Ihto and Sauer present crystals for single amino acid variants, whereas the claims 1 and 22 are unlimited with respect to the amino acid variations and claims 4-5, 15, 29, 32 are unlimited with the additional amino acids at the N- and/or C-terminal ends of the TACE polypeptide of amino acids 1-477 of SEQ ID NO:8. Furthermore, it is noted that the references of Ihto and Sauer fail to address the variability in crystallization resulting from the use of a "hydroxamate-based" binding partner other than that specifically disclosed in the specification.

That structurally similar polypeptides do not form crystals with similar crystal structures is evidenced by Ingram et al. (*Prot. Eng. Design Select.* 19:155-161, 2006), which teaches crystallization of a TACE catalytic domain with a V353G mutation. According to Ingram, the TACE crystal reported by Maskos et al. "was found to be unsuitable for iterative structure-based design studies" and reports crystals of a TACE catalytic domain with a V353G mutation in complex with inhibitor crystallized in a buffer

0.1M sodium citrate and having space group $P2_12_12_1$ and unit cell dimensions that are distinct from the single working example of the specification (p. 157, column 2).

As noted above, Branden et al. states, "The formation of crystals is also critically dependent on a number of different parameters, including...added...ligands to the protein". In this case, applicant attempts to rely on two references which are related to specific proteins and not broad-based, generalized teachings such as those of Branden et al., Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06 and McPherson (*supra*), which would more likely be expected to apply to the class of proteins as a whole. See also the teachings of Buts et al. (*Acta Cryst* D61:1149-1159, 2005), which teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization". Thus, when taken as a whole, a skilled artisan would recognize the state of the art of the art of protein crystallography was highly predictable at the time of the invention, particularly in view of the teachings of Ihto, Sauer, Branden et al., Drenth et al., Kierzek et al., Wiencek, McPherson, and Buts.

Applicant concedes that crystallography was an unpredictable art at the time of the invention, however, asserts that this does not mandate a conclusion that undue experimentation is required to make and use the full scope of the claimed invention. Applicant argues the examiner ignores the disclosure of "several crystallization conditions" of the TACE catalytic domain. Based on this disclosure, applicant argues the cited teachings of Kierzek are not relevant to the enablement analysis.

Applicant's argument is not found persuasive. Contrary to applicant's position, the examiner has not ignored the disclosure of the specification. Further contrary to applicant's position, the teachings of Kierzek are directly relevant to the enablement analysis and fully support the examiner's position since the structure(s) of the TACE polypeptide and/or "hydroxamate-based" binding partner of the claimed crystals and methods are structurally unlimited. When taken as a whole, it is clear from the state of the art as represented by the references of Ihto, Sauer, Branden et al., Drenth et al., Kierzek et al., Wiencek, McPherson, and Buts that a skilled artisan would have no expectation of achieving a diffraction-quality crystal of a TACE polypeptide and "hydroxamate-based" binding partner other than that disclosed in the specification's working example. In this regard, applicant has presented no objective evidence to the contrary.

Applicant argues the general teachings of Wiencek do not necessarily apply to TACE, since it was crystallized at a "wide range" of pH values, *i.e.*, pH 5.0, 5.4, and 8.7.

Applicant's argument is not found persuasive. The examiner acknowledges that the TACE polypeptide as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells in complex with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine crystallized in a 0.1 M sodium citrate buffer at pH 5.0, 5.4, and 8.7. However, it should be noted that, according to the specification, *only Buffer D* at pH 5.4 "allowed the

production of crystals suitable for X-ray data collection" (p. 34, lines 5-6). Moreover, it is noted that the claims are not so limited to the protein, binding partner, and crystallization conditions of the working example at pp. 33-34. In this case, applicant's argument appears to be valid only if the claims require the TACE polypeptide and "hydroxamate-based" binding partner and specific crystallization conditions used in the specification's working example, which they are not. As noted above, the structure(s) of the TACE polypeptide and/or "hydroxamate-based" binding partner of the claimed crystals and methods are structurally unlimited. Also, with the exception of having sodium citrate, the components, concentration, and pH of the crystallization buffer of the crystallization methods are unlimited. As such, applicant's argument does not appear to be commensurate in scope with the breadth of the claims and contrary to applicant's position, the teachings of Wiencek are directly relevant to the enablement analysis and fully support the examiner's position.

Applicant argues the reference of Branden teaches automated methods for setting up crystallization experiments and methods for producing pure protein samples for crystallization were known at the time of the invention.

Applicant's argument is not found persuasive. While applicant points out that automated methods for setting up crystallization experiments and methods for protein purification were known at the time of the invention, it is unclear as to how applicant perceives these teachings as curing the deficiencies of the instant specification with regard to enabling the full scope of the claimed invention. Applicant is requested to

provide clarification. Moreover, applicant is urged to view the references *as a whole* with respect to the state of the art at the time of the invention.

Applicant argues that in view of the disclosure of the specification and the instant claim amendment, the specification fully enables the full scope of the claimed invention without requiring undue experimentation.

Applicant's argument is not found persuasive. At least for the reasons set forth above and the detailed analysis of the Factors of *In re Wands* as set forth in the prior Office action and reiterated above to account for the claim amendment, particularly with respect to the breadth of the claims, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, the quantity of experimentation needed to make or use the invention based on the content of the disclosure, the examiner maintains that undue experimentation is required to make and/or use the full scope of the claimed invention.

Conclusion

[18] Status of the claims:

Claims 1-5, 7-9, 11-12, 14-22, and 29-36 are pending.

Claims 1-5, 7-9, 11-12, 14-22, and 29-36 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
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Art Unit 1656

APPENDIX A

Chemical structure of hydroxamate group